Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 7, pp. 865-870, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00120-0

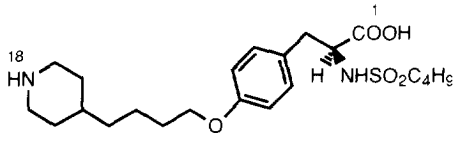
NONPEPTIDE GPIIB/IIIA INHIBITORS. 16. THIENO[2,3-*b*]THIOPHENE α-SULFONAMIDES ARE POTENT INHIBITORS OF PLATELET AGGREGATION

John D. Prugh,* Robert J. Gould, Robert J. Lynch, Guixiang Zhang, Jacquelynn J. Cook, Marie A. Holahan, Maria T. Stranieri, Gary R. Sitko, S. Lee Gaul, Rodney A. Bednar, Bohumil Bednar, and George D. Hartman*

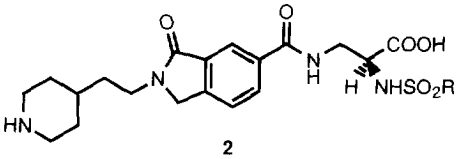
Merck Research Laboratories
Departments of Medicinal Chemistry and Pharmacology, West Point, PA 19486, U.S.A.

Abstract: Centrally constrained thieno[2,3-*b*]thiophene sulfonamides have provided a potent, selective, orally active series of platelet aggregation inhibitors. Compound **21** showed excellent activity in the dog after a single oral dose of 200 μg/kg. © 1997 Elsevier Science Ltd.

One of the latter steps in thrombosis is the aggregation of platelets mediated by fibrinogen binding to the platelet glycoprotein IIb/IIIa (GPIIb/IIIa).[1] This occurs via recognition of the tripeptide sequence, arginyl glycyl aspartate (RGD). The binding of peptide and small molecule RGD mimics to GPIIb/IIIa has been reported to cause inhibition of platelet aggregation.[2] From our own efforts, compound **1** (AGGRASTAT™), a tyrosine derivative with an α-sulfonamide, is now in phase III clinical trials.[3] More recently, several related compounds have been reported,[4a-c] all of which are typified by the lead structure **2,** which utilizes a sulfonamide and a centrally constraining isoindolinone. Compound **2** was shown to be a nanamolar in vitro inhibitor of platelet aggregation and active after oral administration.[4a]

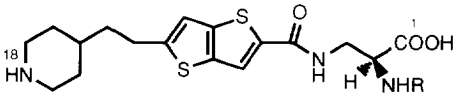


1, AGGRASTAT™

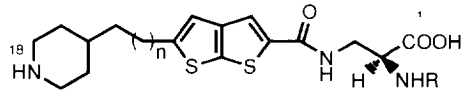


2

With these precedents in mind, and mindful of our prior experience utilizing thienothiophene analogs as membrane permeant agents,[5] we wanted to test whether these dipolar, lipophilic ring systems would offer an opportunity to achieve orally active inhibitors. Accordingly, we decided to prepare the series described by **3** and **4.**



3



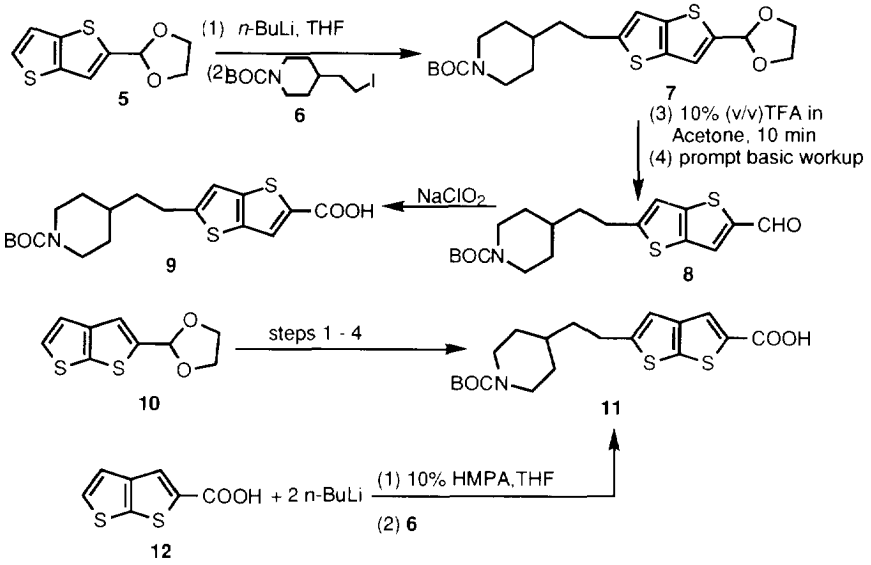
4, n = 1

4a, n = 0, R = SO_2– 

4b, n = 2, R = SO_2– 

Thieno[3,2-*b*]thiophene, **5**, was lithiated in the 5-position[5] and then alkylated with **6**[6] to give **7** in good yield. The delicate task of removing the acetal to liberate the aldehyde **8** in the presence of the BOC group was solved by treating an acetone solution of **7** with TFA (10% final concentration) for 10 min then promptly working up with base. Sodium chlorite oxidation of **8** gave the key intermediate **9**. The thieno[2,3-*b*]thiophene **10**[5] was converted to **11** in a similar fashion.

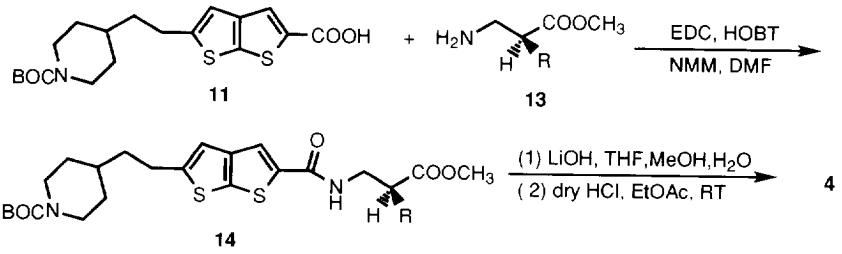
Scheme I



Compound **11** was prepared more directly by treatment of **12**[5] with two equiv of *n*-BuLi in 9:1 THF/HMPA by volume at -78 °C, followed by **6**. In the absence of HMPA, kinetic alkylation in the 3-position predominated, while in the presence of HMPA the ortho lithiation template was disrupted and alkylation occured only in the 5-position.

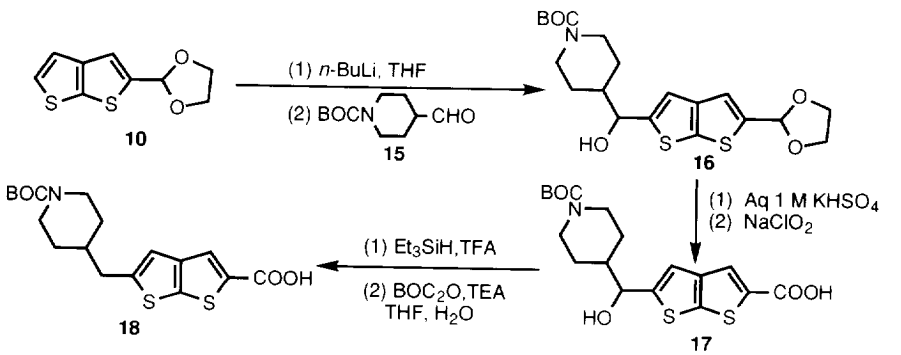
Acid **11** was coupled with the varied amine portion **13**[7,8] using EDC to afford the protected intermediate **14**. Deblocking gave **4**, the final material for testing. The thieno[3,2-*b*]thiophene derivatives **3** beginning with the acid **9**, were prepared in the same way.

Scheme II



To investigate the optimum distance between the thienothiophene and the piperidine ring, we additionally prepared the analogs **4a** and **4b** with one and three methylene units, respectively Analog **4b** was prepared in a manner analogous to that of **4**, except that the final coupling was with **13**, R = 3-pyridylsulfamoyl.

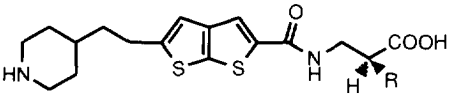
Scheme III



The compound **4a**, with a single methylene unit, merits some discussion. The thieno[2,3-*b*]thiophene, **10**, was lithiated and then treated with known aldehyde, **15**,[9] to give **16** in excellent yield. The acetal was hydrolyzed with 1 M $KHSO_4$ and the resulting aldehyde was oxidized to the acid **17** with sodium chlorite. The secondary hydroxyl group of **17** was reduced by treatment with Et_3SiH in TFA for 6 days; and as expected, the BOC group was also removed. The BOC group was readily reinstalled to give **18**, which was

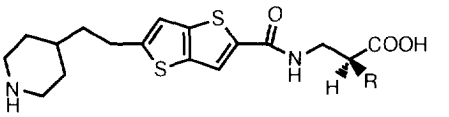
coupled with **13**, R = 3-pyridylsulfamoyl, and deblocked to give the final product **4a**. When these compounds were assayed for inhibition of platelet aggregation, **4b** had IC_{50} = 21 nM, **4a** had IC_{50} = 23 nM, and **4**, R = 3-pyridylsulfonyl, had IC_{50} = 8 nM,[10] supporting synthetic efforts in the series possessing the ethylene spacer.

Table I. α-Substituted Thieno[2,3-*b*]thiophene Analogs of **4**.[11]



Compound	R	Inhibition of Platelet Aggregation IC_{50} (nM)	SPA-A[4] nM	K_D[4] nM
19	$NHSO_2$-(2-thienyl)	9	0.04	0.15
20	$NHSO_2$-(4-Cl-phenyl)	11	0.09	0.026
21	$NHSO_2$-phenyl	8	0.03	0.023
22	$NHSO_2C_4H_9$	32	0.12	5.6
23	H	410	48	ND
24	$NHCONHCH_2$-phenyl	76	1.9	94

Table II. α-Substituted Thieno[3,2-*b*]thiophene Analogs of **3**.[11]

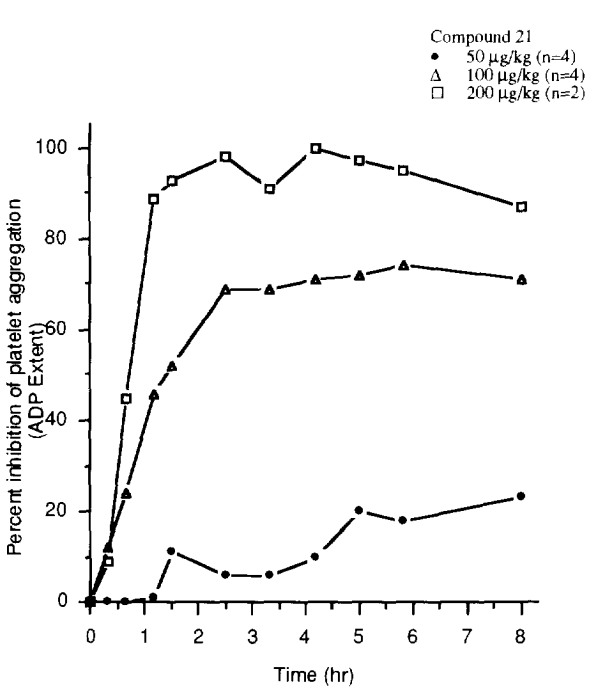


Compound	R	Inhibition of Platelet Aggregation IC_{50} (nM)	SPA-A[4] nM	K_D[4] nM
25	$NHSO_2$-(2-thienyl)	13	0.04	0.092
26	$NHSO_2$-(4-Cl-phenyl)	ND	ND	ND
27	$NHSO_2$-phenyl	8	0.08	0.15
28	$NHSO_2C_4H_9$	10	0.21	3.0
29	H	500	ND	~600
30	$NHCONHCH_2$-phenyl	36	2.6	33

As shown in the Tables, the aryl- and alkylsulfamoyl analogs were more potent inhibitors of platelet aggregation than the ureas and unsubstituted parents. The concentration of GPIIb/IIIa sites on platelets in the test milieu was about 20 nanomolar, so there is an experimental floor to the data. To verify the relative activity of the most potent compounds, the in vitro SPA-A[4d] and K_D[4e] values were determined and these data are in general agreement with the relative potencies of the initial platelet aggregation data. Again, the arylsulfamoyl analogs appeared to be the most potent.

The antiplatelet behavior of compounds was appraised by measuring ex vivo inhibition of platelet aggregation after oral administration to dogs. In the dog, compound **21** showed excellent oral activity that was characterized by >80% inhibition of aggregation throughout 8 h with a 24 h inhibition of 50% at an oral dose of 200 μg/kg. This data suggests the potential for once a day oral dosing.

Figure 1. Effect of once-daily administration (gastric lavage) of **21** at three dosage levels on the extent of ex vivo platelet aggregation in response to ADP (10 μM ADP + 1 μM epinephrine) in conscious dogs.



Acknowledgments: The author would like to thank Jean Kaysen and Joy Hartzell for their assistance in preparing the manuscript.

References

1. (a) Philips, D. R.; Charo, I. F.; Parise, L. V.; Fitzgerald, L. S. *Blood* **1988,** *71*, 831. (b) Philips, D. R.; Kieffer, N. In *Annu. Rev. Cell Biol.*; Palade, G. E., Ed.: Annual Reviews: Palo Alto, 1990; Vol. 6, pp 329-357.
2. Cook, N. S.; Kottirsch, G.; Zerwes, H.-G. *Drugs Fut.* **1994**, *19*, 135.
3. Hartman, G. D.; Egbertson, M. S.; Halczenko, W.; Laswell, W. L.; Duggan, M. E.; Smith, R. L.; Naylor, A. M.; Manno, P. D.; Lynch, R. J.; Zhang, G. A.; Chang, C. T-C.; Gould, R. J. *J. Med. Chem.* **1992**, *35*, 4640.
4. (a) Egbertson, M. S.; Hartman, G. D.; Gould, R. J.; Bednar, B; Bednar, R. A.; Cook, J. J.; Gaul, M. A.; Holahan, M. A.; Libby, L. A.; Lynch Jr., J. J.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Vassallo, L. M. *Bioorg. Med. Chem Lett.* **1996,** *21*, 2519. (b) Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D. *J. Med. Chem.* **1996**, *39*, 4583. (c) Halczenko, W.; Cook, J. J.; Holahan, M. A.; Sitko, G. R.; Stranieri, M. T.; Zhang, G.; Lynch, R. J.; Lynch, Jr., J. J.; Gould, R. J.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1996**, *22*, 2771. (d) SPA-A - ED_{50} Measured by competition with [^{125}I]-L-692,884 for binding to purified GPIIb/IIIa coated onto yttrium silicate Scintillation Proximity Assay Fluomicrospheres. (e) K_D - Measured by competition with fluorescent ligand L-762,745 for binding to resting human gel filtered platelets using flow cytometry. Values are the average of three measurements.
5. Prugh, J. D.; Hartman, G. D.; Mallorga, P. J.; McKeever, B. M.; Michelson, S. R.; Murcko, M. A.; Schwam, H.; Smith, R. L.; Sondey, J. M.; Springer, J. P.; Sugrue, M. F. *J. Med. Chem.* **1991**, *34*, 1805.
6. (a) Egbertson, M. S.; Chang, C. T-C.; Duggan, M. E.; Gould, R. J.; Halczenko, W.; Hartman G. D.; Laswell, W. L.; Lynch, J. J. Jr.; Lynch R. J.; Manno, P. M.; Naylor, A. M.; Prugh, J. D.; Ramjit, D. R.; Sitko, G. R.; Smith, R. S.; Turchi, L. M.; Zhang, G. *J. Med. Chem.* **1994,** *37*, 2537. (b) Compound **6** was prepared from *N*-Boc-piperidyl ethyl alcohol[6a] using standard conditions.
7. Egbertson, M. S.; Bednar, B.; Bednar, R. A.; Hartman, G. D.; Gould, R. J.; Lynch, R. J.; Vassalo, L. M.; Young, S. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1415.
8. Egbertson, M. S.; Homnick, C. F.; Hartman, G. D. *Synth. Commun.* **1993**, *23*, 703.
9. Jacobs, R. T.; Ohnmacht, C. J.; Trainer, D. A., U.S. Patent 5,399,568, 1995.
10. Full discussion of this important compound will appear in a subsequent paper.
11. All compounds were characterized by NMR; TLC; HPLC; C,H,N analysis and/or HRMS.

(*Received in USA* 24 *December* 1996; *accepted* 26 *February* 1997)